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SOME OBSERVATIONS ON THE BEHAVIOR OF THE AUTOMATIC RESPIRATORY AND CARDIAC MECHANISMS AFTER COMPLETE AND PARTIAL ISOLATION FROM EXTRINSIC NERVE IMPULSES.

By G. N. STEWART.

[From the Physiological Laboratories of Western Reserve University and the University of Chicago.]

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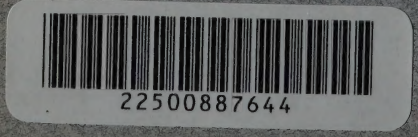

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MORE than ten years ago I began a series of observations on the consequences of simultaneous and successive division of the vagi. Although the theme is a somewhat hackneyed one, the contradictory statements of fact, and especially the conflicting interpretations of the observed facts in the literature, seemed to justify a renewed investigation. Only very brief references to some of the results have hitherto been published.[1] In the meantime experiments made in conjunction with some of my pupils[2] on the partial or complete isolation of the respiratory and other bulbar centres by anæmia, sometimes combined with section of both vagi and of the "upper paths," have given these observations a new interest. Therefore I desire to put them on record in greater detail and to discuss their bearing on our more recent work, some further points in which may advantageously be considered in this connection.

[1] STEWART, G. N.: American year book of medicine, 1901, p. 548; Science, 1905, xxi, p. 889.

[2] STEWART, GUTHRIE, BURNS and PIKE:, Journal of experimental medicine, 1906, viii, p. 289. STEWART and PIKE: This journal, 1907, xix, p. 328; xx, p. 61.

The extensive literature of bilateral vagotomy has been well summarized by Pierre Herzen [3] and Boruttau,[4] and only such papers as bear upon the observations now communicated will be referred to here. The classical clinical picture presented by such animals as the dog, cat, and rabbit, when they have suffered division of both vagi in the neck, is too well known to need description. The slow, deep respiration, in which the duration of inspiration greatly exceeds that of expiration, the rapid heart beat, the frequent vomiting or regurgitation, the progressive emaciation in animals which survive for more than a day or two, as dogs often do, and the terminal double pneumonia which so frequently cuts off the animal, are very familiar phenomena. It is the way in which these symptoms are produced, their permanence, their relative importance in bringing about the fatal result, and the constancy of the latter, particularly when an interval has been allowed to elapse between the division of the two vagi, which have chiefly been subjects of discussion and dispute. Practically everybody is agreed that in animals like the dog which not infrequently survive for a considerable time (several weeks, or occasionally months) the pulse rate tends to return towards the normal. But there is by no means the same unanimity as regards the respiration, some writers asserting that it gradually tends to increase in rate, while others maintain that the slow, deep respiration established immediately on the elimination of the pulmonary vagus fibres is not essentially modified as time goes on. It may at once be stated that in a series of more than fifty dogs, except in those rare instances where the animals survive for an indefinite period the section of both vagi, I have seen no such tendency to increase in the respiratory rate as has been described, for instance, by Nikolaides,[5] in dogs when an interval was allowed to elapse between the division of the first and second vagi, even when the animals eventually died from the consequences of the vagotomy. For instance, in the

Experiment of January 9, 1897, a fox terrier, whose vago-sympathetics were simultaneously divided in the neck, lived 31 days, being fed at first by rectal enemata of eggs beaten up in milk. It received food by the mouth for the first time 8 days after the operation. As shown in Table I, the pulse rate, which before the section, with the animal under morphia, was 65

[3] Herzen, Pierre: Thèse, Lausanne, 1897.
[4] Boruttau: Archiv für die gesammte Physiologie, 1895, lxi, p. 39.
[5] Nikolaides: Archiv für Physiologie, 1905, p. 465.

a minute and after the section 154, had diminished by the fourteenth day to 110. The rate of respiration, which was 15 a minute before section (under morphia) and 11 immediately after section, never on succeeding days rose higher than 10, and was usually lower, except on one occasion when the animal was excited by seeing a mouse, when it reached 12½.

TABLE I.

Days since operation.	Pulse.	Respiration.	Ratio.	Days since operation.	Pulse.	Respiration.	Ratio.
2	145	10	14.5	25	110	6 2	17.7
3	132	8	16.5	"	145[1]	12.5[1]	11.6
7	135	10	13.5	26	136	7.0	19.4
9	120	9	13.3	"	128	8.0	16.0
13	120	10	12 0	27	128	8.0	16.0
14	110	10	11.0	28	94	8.0	11.7
16	114	8	14.2	29	147	6.3	23.7
18	136	9	15.1	"	148	..	....
20	136	10	13.6	"	154	..	....
21	134	10	13.4	30[2]	158	7.5	21.0
23	130	10	13.0	31	144	8.5	16.9
24	134	..	....	"	137	8.5	16.1
"	128	7	18.3	..	..	..	....

[1] In excitement caused by sight of mouse. Some of the respirations are shallow. Counting only the deep respirations, the respiratory rate is not increased.
[2] The dog is very weak.

The ratio of the heart rate to the respiratory rate, which was 4.3 to 1 before section was never less than 11 to 1 afterwards and nearly always considerably more. In another fox terrier operated on at the same time and kept under the same conditions, except that it ate for the first time on the third day, the pulse rate soon after the operation was 160 and the rate of respiration 10 (ratio, 16 : 1). The pulse rate on the ninth day had sunk to 118, but the respiration was only 8 (ratio, 16 : 2.1). On the twelfth day the numbers were 120 and 7 (ratio, 17.1 : 1). It died on the thirteenth day.

In a collie on the evening before operation the pulse and respiratory rates were 78 and 22 respectively (3.5 : 1); on the morning before operation 82 and 28 (2.9 : 1); under morphia and ether 96 and 16 (6 : 1); after section of the first vagus 126 and 20 (6.3 : 1); after section of the second vagus 170 and 18 (soon 14); on the day after the operation 158 and 11.6 (13.6 : 1); on the second day 160 and 16 (10 : 1), on the fifth day 143 and 9.3 (15.4 : 1), on the seventh day 140 and 11.4 (12.2 : 1), on the twelfth day 128 and 16 (8 : 1), on the thirteenth day 117 and 12 (9.7 : 1). The animal died on the fourteenth day.

In a spaniel the pulse and respiratory rates on the evening before operation were 94 and 16 respectively (5.9 : 1); on the morning before operation 84 and 18 (4.6 : 1); under morphia and ether 68 and 18 (3.8 : 1); after section of the first vagus 140 and 10 (14 : 1); immediately after section of the second vagus 160 and 15 (10.6 : 1); on the first day after the operation 188 and 6.7 (28 : 1); on the second day 170 and 9 (19 : 1); on the fifth day 152 and 6.8 (22.3 : 1); on the sixth day 144, and 6.6 (21.8 : 1); on the seventh day 146 and 7.8 (18.7 : 1); on the ninth day 154 and 9 (17.1 : 1); on the day of its death (the eleventh day) 151 and 7 (21.5 : 1).

Not only does the rate of respiration show a relatively high degree of stability in one and the same dog after bilateral vagotomy, but there is a far smaller range than normal in the frequency in different dogs in the absence of the pulmonary regulating impulses. This is well illustrated in Table II, which gives the pulse rates, the respiratory rates, and the ratios between them before section, after section of one vagus, and after section of both in twenty-three animals, all of which died. In only one case was the rate of respiration more than 12, after section of both vagi, when the immediate excitation caused by the section had passed off. In eighteen cases it was 9 or less; in four cases 4 or 5. In 50 per cent of all the cases the rate was 6 to 8. The ratio of pulse to respiratory rate was invariably much greater than the normal, although, owing to the tendency of the pulse rate to diminish in animals which survived more than a few days, the ratio tended towards the normal as time went on, but without ever reaching it, except in those rare cases of complete recovery already mentioned.

It is an interesting question how this relative stability in the respiratory frequency, which is notoriously susceptible to so many influences in the normal animal, is maintained after elimination of the vagi. Some have laid stress on the vicarious control of the

TABLE II.

SECTION OF BOTH VAGI IN DOGS.

No. of experiment.	Pulse rate.			Respiratory rate.			Ratio of pulse to respiration.		
	Before section.	After section of one vagus.	After section of second vagus.	Before section.	After section of one vagus.	After section of second vagus.	Before section.	After section of one vagus.	After section of second vagus.
1	79	140	160	15	10	15	5.2	14	10.6
			188[1]			6.7[1]			25.0[1]
2	96	126	170	14	20	18	6.8	6.3	9.4
			158[1]			11.6[1]			13.6[1]
3	65		154	15		11	4.3		14.0
4	118		164	20		4	5.9		41.0
5	51		152	14.2		5.8	3 6		26.0
6	50		144	8.4		7	5 9		20.5
7	78	90	151	24	15	6	3 2	6	25.1
8	36	58	160	22	16	5	1.6	3.6	32
9[2]	45		190	15		12	3.0		15.8
10			205			5			41.0
11[3]	92	147	191	14	17	10	6.5	8.6	19 1
12[3]	69	130	165	11	19	8	6.2	6.8	20.6
13	80	120	145	18	8	8	4.4	15	18.1
14[4]	68		172	10		7	6.8		24 5
15	70	72	104	16	12	9	4 4	6	11.5
16	108	72	116	29	24	13.5	3.3	3	8.6
17	77	86	150	13	10.5	9	5.9	8.2	21.4
18	46		92	18		10	2.5		9.2
			156[1]			7[1]			22 3[1]
19	60	88	140	16	11	8	3.7	8	17.5
20	70	72	104	16	12	9	4.4	6	11.5
			154[5]			8[5]			19.2[5]
21	56	135	180	14	10	6	4	13.5	30.0
22	66	72	80	33	10	4	2	7.2	20
			120[6]			3[6]			40[6]
23[4]	36	68	160	8	19	9	4.5	3 6	17.8

[1] After one day. [2] Vagi crushed thoroughly without being divided.

[3] Pup three months old.

[4] Second vagus divided fifty-nine days after the first. The counts were made during anæsthesia with morphia and ACE mixture.

[5] Seven hours after operation. [6] After five or six minutes.

"higher paths." We have seen good reason to believe not only that these paths from parts of the brain lying higher than the bulbar respiratory centre do exert an influence upon that centre after section of the vagi (in cats), but that they are normally active since section of them, the vagi being intact, produces some diminution in the frequency of the respiratory movements, contrary to Marckwald's observations (on rabbits).[6] Yet the stability in the rate of the respiratory discharge is mainly due, we believe, not to the development of an effective extrinsic regulation which takes the place of the regulation normally exercised by the Hering-Breuer fibres, but to the relative isolation of the bulbar centre from extrinsic impulses, which permits its "native" automatic or autochthonous rhythmical discharge to dominate the situation. For nothing is more striking than the diminished susceptibility of the respiratory rhythm of the vagotomized dog to such influences, including psychical disturbances, as powerfully affect the respiration of the normal animal, although experimental stimulation of the central end of the vagus or of the sciatic still produces a great effect. In the experiment of January 9, 1897, for instance, already quoted, the intense psychical excitation produced by the sight of a mouse, which obviously aroused the keenest interest on the part of the dog, only increased the respirations to 12½ a minute, and this at a time when the animal was in fairly good condition, on the twenty-fifth day after the operation. It would almost seem as if the bulbar centre in the absence of vagus control developed its own rhythm to such a degree that it remained stable in the presence of extrinsic excitations which in its normal condition would have caused a marked alteration in it.

In conjunction with Dr. F. H. Pike[7] I have recently brought forward fresh evidence that the bulbar respiratory centre is not only capable of such automatic rhythmical discharge at a point in the resuscitation of the brain and cervical cord after a period of anæmia when as yet all the afferent paths leading to it, including the vagi, are still incapable of conduction, but that the initial rate of discharge under these circumstances is remarkably constant. The character of the respiration at this time irresistibly reminds one of the respiration after double vagotomy. Although these resuscitation experiments were made mainly on cats, with a few observations

[6] MARCKWALD: Zeitschrift für Biologie, 1887, xxiii, p. 149; 1890, xxvi, p. 260.
[7] STEWART and PIKE: This journal (*loc. cit.*).

on rabbits and very few on dogs, which are not suitable on account of the free collateral circulation to the brain through the intra-vertebral vessels, it cannot be doubted that in some points they throw light on each other. I have the less hesitation in so applying them that the practically constant initial rate of discharge (about 4 a minute) of the resuscitated respiratory centre of the cat agrees extremely well with the rate observed by Loewy [8] in rabbits, after section of the vagi and the brain stem above the bulb, and with the rate observed by Katschkowsky [9] and by myself (Table II) in a certain number of vagotomized dogs. The constancy of this rhythm points to its dependence upon a fundamental property of the nervous elements in which it originates. A qualitative similarity between the respiratory centres of animals even of widely distant groups is universally admitted. There is nothing improbable in the existence of a quantitative similarity between not very widely separated mammals. It is a very natural supposition that in a certain number of animals, especially when fully anæsthetized, the higher parts of the brain should be exerting so little influence that section of the vagi alone is sufficient to bring about that degree of isolation of the respiratory centre from afferent impulses which is associated with the development of its fundamental rate of discharge, although in the majority the influence of the higher paths must still be removed before the necessary isolation is attained.

The relative constancy of the discharge of the respiratory centre (in cats) so long as it is isolated from the afferent impulses is well illustrated in the experiments cited in Table III, where the isolation was accomplished by subjecting the brain and cervical cord to a period of anæmia, and in those of which Table IV gives some specimens, where, in addition to the anæmia, the brain stem was divided at the posterior boundary of the posterior corpora quadrigemina or farther forward. In some cases both vagi were also cut, and occasionally the spinal cord as well in the lower cervical region. In determining the initial rate it must be remembered that when the return of function of the respiratory centre is very rapid, as after relatively short occlusions, the rate obtained by counting several respirations or even by measuring the interval between the first two may be greater than the true initial rate, since the afferent paths may begin to be opened up even in this short interval.

[8] Loewy: Archiv für die gesammte Physiologie, 1888, xlii, p. 245.

[9] Katschkowsky: Archiv für die gesammte Physiologie, 1901, lxxxiv, p. 6.

TABLE III.

OCCLUSION OF HEAD ARTERIES IN CATS.

Date of experiment.	Length of occlusion in minutes.	Time after release in minutes.	Rate of respiration per minute.	Date of experiment.	Length of occlusion in minutes.	Time after release in minutes.	Rate of respiration per minute.
1905.				1907.			
April 19	16	30[1]	4	Feb. 23	8	6[1]	
		34	12			7	5.80
		37	12[2]			11	8
		44	16			13	20
						27	41.90
April 29	15	8[1]					
		11	16	2d occlusion	7	3.30[1]	7.20
		74	208			8.30	14.50
		183	224			19	49.10
				Feb. 27	18.30	13[1]	3.50
May 2	30[3]	14.15[1]	4			16	3.50
		18.15	3.75			53	7.50[4]
		21.15	6.30				
		22.15	13.30				
		360	84	March 12	9	3.15[1]	6
						3.35	10.90
May 23	51	31[1]	4	March 13		3.45[1]	16.80
		41	24[2]				
		45	30	2d occlusion	7	10[1]	6.20
May 27	45	40.30[1]	3 to 4	March 18	7	+3.30[1]	5
		42.30	3.30			6	7
		50.30	7	March 19	15.15	7[1]	6[5]
		57.30	7.30[2]				
		67.30	6.80	March 20	15	11[1]	7.50
		75.30	7.70				
				April 24	8.20	7.40[1]	
June 7	31	9[1]	4			9	3.20
		26	13.50[2]			10	6.80
		27	18	March 30	16.10	4	9.10[6]
		32	28				
		370	112	2d occlusion	11	11.30[1]	4.10
1907.						12.30	4.10
Feb. 20	12	6[1]	4.30			15	4
						22	7
Feb. 22	7	17[1]				25	7.20
		23.30	6				

[1] First respiration.
[2] After stopping the artificial respiration.
[3] Imperfect occlusion.
[4] Both vagi had been cut.
[5] Exactly 6 large respirations a minute with apparently an additional small movement between each pair of large ones.
[6] This is not the initial rate, as the respiration had returned earlier, at a time not definitely noted.

The constancy of the initial rate in resuscitation does not depend on a constant stimulation of the centre connected with such physical factors of the circulation as the blood pressure, since it is equally observed in animals during resuscitation after a period of cerebral anæmia when the general arterial pressure is much lower than

TABLE IV.

SECTION OF THE BRAIN ABOVE THE BULB AND OCCLUSION OF HEAD ARTERIES IN CATS.

Date of experiment.	Length of occlusion in minutes.	Time after release in minutes.	Rate of respiration.	Remarks.
1907.				
June 26	13	9[1]	..	One minute later stimulation of the brachial causes distinct acceleration of respiration.
		11	5.5	
July 3	10	33[1]	..	Exactly the same rate during stimulation of the brachial or the vagus.
		39	4.3	
		41	4.3	
		43	4.3	
		47	4.5	
July 10	10	4[1]	..[2]	
		8	4.6	
		11	7.0	
		13	6.0	
		15	6.6	
		20	11.0	After stopping the artificial respiration. Spinal cord divided and aorta clamped below the diaphragm.
		32	..	
		75	9.0	

[1] First respiration.

[2] Section of both vagi produces no effect on the respiration.

normal (Table III), in animals after section of the vagi and the brain stem above the bulb without cerebral anæmia when the blood pressure may be normal, and in animals after cerebral anæmia when the blood pressure has been kept abnormally high by ligation of the aorta just distal to the origin of the head arteries or at any point between this and the lower surface of the diaphragm (Table V). Nor is it necessarily dependent on any particular chemical condition of the blood, its content of carbon dioxide or oxygen for example, since in resuscitation after cerebral anæmia, with artificial respiration of constant rate and depth, the spontaneous respiratory movements return in different experiments at very different intervals after the restoration of the circulation, and the

time of their return and their initial frequency are quite independent of the rate of the artificial respiration or of the total ventilation produced by it. It is easy to see that if the respiratory discharge depends on stimulation by the carbon dioxide of the blood the "excitability" of the centre must be restored before discharge can take place. Perhaps the tension of the carbon dioxide in the centre must be reduced to a certain point before this excitability is restored. In any case the initial rate must, as has already been remarked, be connected with some internal property of the respiratory centre, and the fact that whether the respiration returns early or late in resuscitation, after a long or short period of anæmia, its rate is at first the same, suggests that the property on which this rhythm depends is a very fundamental one. For it is impossible to suppose that in every particular the chemical or physical condition of the respiratory centre is the same at the moment when it first resumes its discharge, whether the occlusion has been long or short, single or repeated, the return of respiration tardy or prompt, the animal deeply or lightly narcotized before the occlusion, the blood at or near the normal temperature or decidedly below it, the animal young or old, a rodent or a carnivore.

An interesting observation illustrating the relation of the circulation to the respiratory centre during resuscitation may generally be made in experiments where the aorta is clamped below the origin of the head arteries, so that a relatively high pressure is restored in the head immediately on release of the head arteries. Respiration, having returned, ceases after a time, as is very often the case also where the aorta has not been clamped, a state of apnœa being induced. When the aorta is now released so as to lower the blood pressure in the head, the respiratory movements soon return, as in the experiment of March 30, 1905 (Table V). It would be of interest to determine whether heat dyspnœa can be obtained immediately after the return of respiration in resuscitation, and whether the rate of discharge of the centre is affected by increase of temperature before the afferent paths are opened up; also whether the time of appearance of the first respiration is influenced by the temperature of the blood. But hitherto I have not been able to test these questions. As the afferent paths, especially the pulmonary vagus paths, begin to open up in resuscitation, there is an increase, often abrupt, in the mean rate of discharge (Table VI in addition to Tables III and V). There is an equally significant diminution

in its stability, stimulation of the afferent fibres not only in the vagi but in the ordinary peripheral nerves affecting it more and more. At a certain stage in resuscitation the influence of the incoming

TABLE V.

OCCLUSION OF THE HEAD ARTERIES IN CATS AFTER LIGATION OR CLAMPING OF AORTA DISTAL TO ORIGIN OF LEFT SUBCLAVIAN.

Date of exp.	Length of occlusion in minutes.	Time after release in minutes.	Rate of respiration.	Remarks.
1905.				
March 29 (I)	10	5.10[1]	4	Half-grown cat. Internal mammaries tied.
		11.30	4	Jaws, tongue, forelimbs, and ribs move strongly in resp., but not the diaphragm
		21.30	..	Stim. of left phrenic causes no cont'n of the diaphragm, nor does direct stim.
		25.30	20	Resp. now mainly head and jaw move'ts.
		46.30	..	Released aorta.
		48.30	20	
March 29 (II)	20	5[1]	3 to 5	Half-grown cat. Internal mammaries tied. 20 sec. between first and second respiration, then respiration goes on at 5 a minute. Includes head and chest.
		7	6	
		11	8	
		13	12	Including some small resp'y mov'ts, one of which sometimes precedes a deep one.
		29	33.3	Natural respiration exactly synchronous with artificial.
		79	..	Diaphragm contracts on direct stimulation but not on stimulation of phrenic.
March 30	24.30	27.30[1]	5 (exactly)	The diaphragm does not participate in the movements, though direct or indirect stimulation of it causes contraction.
		30.30	11.2	
		39.30	12	
		44.30	..	Respiration has ceased.
		76.30	..	Diaphragm still contracts on stimulation of phrenic.
		92.30	..	
		95.30	..	Released aorta. Resp. soon started.
		97.30	18	
April 3	50	67.30[1]	..	Prepared cat.
		70.30	about 3	
		108.30	5	
1907		119.30	26	
March 7	7.15	1.45[1]	3.30	
		4	6	
Second occlusion . .	..	26.30[1]		
		28.30	6.2	
		35	7.9	
March 29	7.45	+1[1]	4.3	
April 2	5	+1.30[1]		After 1½ minutes asphyxia produced by clamping the trachea, respiration is 5 a minute. After 2½ minutes asphyxia, 6.5 a minute.
		4	3.6	
Second occlusion . .	6	−4[1]	..	After ½ minute asphyxia respiration is 2 a min., after 2½ minutes asphyxia 6 a min.

[1] First respiration.

impulses from the vagi comes so to dominate the automatic rhythm that in some experiments the natural respiratory movements have been seen to acquire precisely the same frequency as the artificial

TABLE VI.

EXPERIMENT MAY 13, 1905. CAT. TIME OF OCCLUSION, 60½ MINUTES.

Time after release.	Rate of respiration per minute.	Time after release.	Rate of respiration per minute.
33½ m.[1]	2 to 4	7 h. 47 m.	16
37½ m.	9[2]	8 h. 19 m.	16
44½ m.	8[2]	9 h. 15 m.	19
52½ m.	4 3[3]	9 h. 21 m.	22
3 h. 24 m.	10.7	9 h. 26 m.	18
3 h. 30 m.	14	9 h. 47 m.	30
4 h. 7 m.	14	10 h. 4 m.	30
5 h. 37 m.	14	10 h. 32 m.	19
6 h.	14	11 h. 12 m.	23
6 h. 12 m.	13	11 h. 57 m.	23.5
6 h. 29 m.	14.5	12 h. 47 m.	6.5
6 h. 51 m.	16		

[1] First respiration. The second respiration followed 30 seconds after the first, the next five at intervals of 15, 30, 15, 10, and 12 seconds respectively. Then the rate became nine a minute, half of the respirations being weak and the rest very strong. Each weak respiration began in 7 seconds, and each strong one in 12 seconds, from the beginning of the last respiration.

[2] Strong and weak alternately as before.

[3] Very strong, without any weak respirations interposed.

At 3 h. 12½ m. artificial respiration was stopped. From 9 h. 15 m. till 10 h. 31 m. ether was administered to control the spasms. At 11 h. 12 m. ether was again begun and continued till 15 h. 22 m. after release, when the animal died of ether poisoning.

respiration and to persist at exactly this rate for some time after the stoppage of the artificial respiration, an artificial rhythm having been, so to speak, impressed upon the respiratory centre by the rhythmical excitation of the pulmonary vagus fibres. For example, in the

Experiment of March 24, 1905, after an (imperfect) occlusion of 30 minutes in a young female cat, respiration had returned for several minutes,

when it was noticed that the natural respiratory movements were exactly synchronous with the artificial respiration, which was at the rate of 42 a minute. Artificial respiration was now stopped, and the animal went on breathing at precisely the same rate for about 25 seconds. This was 14 minutes after the release of the head arteries. Seven minutes later the spontaneous respiration was going on at the rate of 32.4 a minute; 52 minutes after release it was 75; and 80 minutes after release, 171 a minute. In another cat (a large adult male), after a perfect occlusion of 5 minutes, respiration returned 35 seconds after release. On stopping the artificial respiration, 8½ minutes after release, the cat went on breathing for 3½ minutes at exactly the same rate (42 a minute). The respirations then became quicker, increasing to 54 a minute 14 minutes after release, and to 128 a minute 38½ minutes later. In the experiment of March 22, 1905, in a very large adult male cat, after an imperfect occlusion of 10⅝ minutes, spontaneous respirations did not disappear, and soon after release it was observed that they were proceeding at exactly the same rate as the artificial respiration (48 a minute). In the first minute or two after release the spontaneous respiration ceased if the artificial was stopped. This was also the case for the last minute or two of occlusion, as if the excitation of the respiratory centre depended upon the afferent impulses set up in the vagi by the movements of the lungs. When the artificial respiration was stopped, 5⅞ minutes after release, the natural respiration went on with exactly the same rhythm for a little time, and then, in less than a minute, began to get quicker.

Much evidence has been obtained in the course of this work that, great as the influence of afferent impulses on the rate and character of the bulbar respiratory discharges is, it is, as a rule, only capable of being exerted when the respiratory centre is already discharging itself automatically. There are, however, conditions in which a perfectly quiescent respiratory centre can be roused to discharge by the excitation of afferent nerves, as in the following experiment.

Experiment of November 5, 1890. — Dog weighing 13 kilos received 0.16 gm. morphia hydrochlorate subcutaneously. Five hours later, stimulation of the central end of the anterior crural nerve caused violent respiratory movements. Chloroform was now administered, and the respiration stopped. Stimulation of the anterior crural always causes respiration to begin and to go on again violently for a little time. The animal struggles also, but respiration soon ceases. The pulse is much accelerated. The corneal reflex is well marked, and there are occasional swallowing movements. Obviously the bulbar centres are not all paralyzed. Yet, if left

alone, respiration soon ceases. Air enters the lungs freely, and there is no obstruction in the trachea. If the condition is one of apnœa, it has not been induced by artificial respiration, since none has been employed. The animal was kept alive for more than an hour by occasional stimulation of the anterior crural, a burst of respirations following each stimulation, but spontaneous breathing never returned, although no chloroform was given from the time the respiration first stopped. At last the animal was killed by bleeding. After blood had ceased to flow, respiratory movements began spontaneously and continued for a minute or two.

This seems to show that the respiratory centre, injured too much by the chloroform and morphia to act spontaneously and only discharged itself when stirred up by the arrival of afferent impulses, recovered its natural automatic power when the blood was drawn off, either because some of the still circulating poison was withdrawn, or because the anæmia increased temporarily the excitability of the centre or its power of developing autochthonous stimuli, or the intensity of the "blood stimulus."

S. J. Meltzer and J. Auer[10] have found that magnesium salts produce such an effect on the respiratory centre that the respiration stops, although if the dose is not too great stimulation of the sciatic may cause respirations to be discharged. The fact that in such conditions the respiratory centre can be roused to activity by afferent impulses is, of course, no more an argument against its normal automaticity than the existence of conditions in which a perfectly quiescent heart can be caused to beat by stimulating its augmentor nerves is an argument against the automaticity of the heart's beat. I showed long ago[11] that the frog's heart when reduced to complete standstill by cautiously heating it in salt solution, can be caused to beat by stimulating the cervical sympathetic, even while the temperature necessary for standstill continues to be maintained. A long series of beats ensues which much outlasts the stimulation. This, as well as the distance of the sympathetic from the heart, eliminates the possibility of escape of current on to the heart being the cause of the contractions, — a criticism to which Schelske's observations[12] on the effect of stimulation of the frog's vagus during

[10] Meltzer, S. J., and Auer, J.: This journal, 1905, xiv, p. 366; 1906, xv, p. 387.

[11] Stewart, G. N.: Journal of physiology, 1892, xiii, p. 93.

[12] Schelske: Über die Veränderungen der Erregbarkeit durch die Wärme, Heidelberg, 1860.

heat standstill of the heart are justly exposed, since he states that the stimulation causes a tetanic condition and that single induction shocks are followed by single contractions. My observations constitute, I believe, the first satisfactory demonstration that the augmentor nerves of the heart have the power of causing beats when the heart is entirely at rest, although they seem to be unknown to H. E. Hering, who long afterwards [13] demonstrated a similar action of the accelerantes in mammals on hearts reduced to standstill in various ways. He incidentally observed a similar rousing of auricles and ventricles to activity in a dog, some years earlier,[14] but specifically states that he could not tell whether the veins might not still have been pulsating at the time of the stimulation. Hering rightly considers that Schelske's vague statements do not constitute a demonstration of this action for the frog's vagus.

S. A. Matthews [15] has shown that, in the standstill of the dog's heart produced by magnesium salts, stimulation of the accelerantes causes it temporarily to resume beating.

Another analogy, and an interesting one, between the automatic respiratory and the automatic cardiac mechanism is the sudden and strong return of respiration in resuscitation after cerebral anæmia and the sudden and strong return of the ventricular beat under the influence of direct massage in resuscitation after cardiac failure induced by asphyxia, ether poisoning, and in other ways. For example, in the experiment of May 16, 1905, after an occlusion of 81 minutes the heart was found to have stopped about 16 minutes after release. The chest was opened, the aorta clamped below the origin of the head arteries, direct massage of the heart started, and the animal put into a hot-water box, artificial respiration, of course, being kept up all the time. The auricles began to beat very soon after massage was begun, as usually happens, but the ventricles beat very poorly and intermittently. About 20 minutes after the stoppage of the heart and 15 minutes after the starting of massage, the ventricles quite suddenly began to beat well. No further massage was necessary throughout the experiment. More than five hours later the heart was beating excellently, when the experiment had to be stopped. Here it would seem that the nervous

[13] HERING, H. E.: Zentralblatt für Physiologie, 1905, xix, p. 129; Archiv für die gesammte Physiologie, 1906, cxv, p. 354.

[14] *Ibid.*, 1901, lxxxvi, p. 578; Zentralblatt für Physiologie, 1901, xv, p. 683.

[15] MATTHEWS, S. A.: This journal, 1907, xx, p. 323.

mechanism, if it is nervous, which conducts the impulses from the auricles to the ventricles when its resuscitation reaches a certain point suddenly begins to conduct, just as the respiratory centre when its resuscitation reaches a certain point suddenly begins to discharge. Under the conditions of our experiments the "all or nothing" law appears to apply to the respiratory centre when isolated from afferent impulses as it normally does to the heart.

We might also consider the fact that the respiratory centre, isolated as described, discharges itself not continuously but with a constant rhythm, — a token that, as regards such excitation as is exerted on it by the blood, it possesses a refractory period.

The relative constancy of the heart rate in the first hours or days after double vagotomy in different individuals of the same species and even in the different mammalian species studied, whatever the rate may have been before section, may also be considered analogous to the relative but more marked constancy of the respiratory frequency after isolation of the respiratory centre either from all afferent impulses or from that most influential contingent which reaches it through the vagi. Of course, greater variations are to be expected in the rate of the heart, which is still in connection with the greater part of its accelerator supply and probably even with a certain portion of its inhibitory supply after section of both vagi, than in the rate of respiration after complete elimination of the afferent paths to the bulbar centre. But still the range is singularly narrow after the immediate effects of the section and of the anæsthetic have passed off. What the respective shares of the accelerator mechanism, whose tone has been investigated by Tschirjew,[16] Friedenthal,[17] Hunt,[18] and others, and of the local regulating mechanism in the heart which many writers assume, may be in bringing about the gradual return of the heart rate towards the normal in dogs which survive for some time, cannot be settled at present. There is some evidence that inhibitory fibres may reach the heart by other paths than the vagi, perhaps issuing from the upper thoracic cord with the accelerator fibres,[19] and these, although perhaps normally of comparatively slight importance, may come to play a more important rôle when the main cardio-inhibitory path has been severed.

[16] Tschirjew: Archiv für Physiologie, 1877, p. 116.
[17] Friedenthal: Archiv für Physiologie, 1902, p. 135.
[18] Hunt: This journal, 1899, ii, p. 395.
[19] *Cf.* Friedenthal: *Loc. cit.*

The rate of the heart isolated from all extrinsic innervation and under given conditions of temperature, coronary pressure, and nutrition, appears to be still more constant in individuals of the same species and in different mammalian groups than the rate after elimination of the vagi alone. Taking the point in resuscitation in

TABLE VII.

Date.	Length of occlusion in minutes.	Time after release in minutes.	Blood pressure in mm. of Hg.	Pulse rate.	Date.	Length of occlusion in minutes.	Time after release in minutes.	Blood pressure in mm. of Hg.	Pulse rate.
1907.					1907.				
Feb. 27	18.30	32	158	179	April 5			84	221[3]
(cat)		60.30	124	163	(rabbit)				210[3]
		74	130	171		6.45 (1)	0	58	161
							6.45	112	180
Mar. 5	4.45 (1)	14.15[1]	124	166			12[2]		
(cat)		19.15[1]	120	161			16.45	119	174
							18.15	120	170
Mar. 7	7.15 (1)	7.45	140						
(cat)		18.45	124	150	April 20			94	182[3]
		21.15	120	151	(rabbit)	19.30 (1)	8.30	110	166
		24.45	119	150		(imperf.)			
		38.45[2]	121	144		6 (2)	7.45	48	148
							21	120	163
Mar. 29			184	146[3]			26[2]	110	163
(cat I)	7.45	5	124	165					
(cat II)			158	180[3]					
	9	3.15	60						
		6.30		164					

[1] No reflex inhibition of the heart can yet be obtained.
[2] Reflex inhibition first obtained.
[3] Before occlusion.
A number in parentheses in the occlusion column indicates whether the occlusion was the first or second in experiments in which there was more than one occlusion.

about forty cats (specimens of the data are given in Table VII) at which both the inhibitory and the accelerator mechanisms have not yet recovered their tone while the heart muscle is still in a tolerably normal condition and the pressure and temperature of the blood are not far from normal, the average pulse rate is between 155 and 160. In the few rabbits which yielded results suitable for this determination the average was between 160 and 165. In an experiment on a dog by Tschirjew after elimination of the vagi and the accelerators with the knife I find the average of all the observations is about 151. But if one selects observations where the blood

pressure was within the normal range, the average is higher (155 to 160). The average rate for the twenty-two dogs referred to in Table II after section of the vagi alone is 163, when only observations made after the primary excitation effect of dividing the vagi has passed off are included. The rate for the dog's heart isolated completely from extrinsic impulses must be less than this on account of the accelerator tone. The average of all the observations on a rabbit quoted by Tschirjew I find to be a little over 165. The suggestion is that, under precisely similar conditions, the hearts of the rabbit, cat, and dog when isolated from the central nervous system beat very much at the same rate, just as the respiratory centres of these animals when isolated from all afferent impulses discharge themselves very much at the same rate. Of course such calculations are open to a certain amount of error, and it is possible that careful experiments specially directed to this point, in which the temperature and blood pressure were exactly controlled might show constant differences even in individuals of the same species. But it can be safely predicted that the range would not be found a wide one even between not too distant groups. And without pressing the analogy too much, it may be considered, perhaps, an additional argument in favor of the idea that the mechanism which originates the cardiac rhythm is of the same nature as the mechanism which originates the respiratory rhythm, namely, a nervous one. That is to say, if the relative constancy of the fundamental respiratory rhythm, that of the isolated respiratory centre, is a deep-seated attribute of nervous structures, the existence of a similar constancy in the fundamental cardiac rhythm, that of the heart isolated from extrinsic impulses, is an indication that the seat of that rhythm may be of nervous nature too.

It has been mentioned that as a rare phenomenon a dog both of whose vagi are cut in the neck at the same time may recover and live for an indefinitely long period, comporting himself to all intents and purposes as a normal dog. I have had one, perhaps two, such cases among more than fifty dogs subjected to simultaneous bilateral vagotomy. One of these unfortunately escaped, owing to the carelessness of an attendant, when all danger seemed to be passed and it was gaining weight rapidly, 24 days after the excision of about an inch of each vago-sympathetic. The other was kept for 300 days and then sacrificed for autopsy. The ends of the left vago-sympathetic were found separated by about ½ inch. In the right

vago-sympathetic the seat of the section was indicated by a fine transverse scar visible to the eye, and seen on cutting longitudinal sections after hardening in Muller's fluid embedding in celloidin, and staining by Berkley's "rapid" modification of the Weigert-Pal method [20] to be occupied by scar tissue. Scar tissue free from fat cells occupied the part of the sheath opposite the transverse lesion. The section was complete except for a strand of sheath at the outer side of the nerve, which perhaps was responsible for keeping the two portions of the severed nerve so well in line. Some regeneration appeared to have taken place, since stimulation of the nerve with induction shocks, before death, caused slowing and weakening of the heart. This, however, does not account for the recovery of the animal, since all the serious symptoms had disappeared long before any regeneration could have occurred. For the same reason it cannot explain the rapid return of the pulse rate, the respiratory rate and the ratio between them to the normal (Table VIII). When the animal vomited, as it did repeatedly from the eleventh day after the operation till the end of the third month, it always made the sound associated with that act in the normal dog. The other vagotomized dogs made no sound while vomiting, indicating that apparently in this exceptional dog a portion of the innervation of the glottis had escaped. Slapping the dog's sides elicited the sound of vomiting although he did not actually vomit, and he not infrequently made this sound spontaneously without vomiting. When he did vomit, it was usually only frothy liquid and not more or less digested solid food, as in the case of ordinary dogs. These cases of complete recovery were mentioned in an article written in November, 1900.[21] At the Madrid International Medical Congress of Medicine, in April, 1903, Ocaña showed a dog which, ten weeks after simultaneous section of the vagi in the neck, was in perfect health and remained so for more than six months. After death, he states, the complete division of both vago-sympathetics was verified.

Several observers have supposed that when a considerable interval is allowed to elapse between the section of the two vagi the fatal result is postponed. Nikolaides [22] states that two dogs out of three operated recovered completely when the second vagus was cut 47 days and 57 days respectively after the first. He seems to assert

[20] LEE, BOLLES: Vade-Mecum, 5th edition, p. 403.

[21] STEWART, G. N.: American year book of medicine, *loc. cit.*

[22] NIKOLAIDES: Zentralblatt für Physiologie, xiv, p. 197; xv, p. 482.

that as a general rule large strong adult dogs will survive the operation and recover if it be performed in two stages with such an interval between. Whether the comparatively genial climate of

TABLE VIII.

February 5, 1897. Skye terrier. Pulse in the evening before operation 120, respiration 38 (ratio 3.1); morning before operation, pulse 90, respiration 38 (ratio 2.3); after morphia and ether, pulse 63, respiration 23 (ratio 2.7); after exposure of the vagi, pulse 85, respiration 24 (ratio 3.5); after division of first vagus, pulse 86, respiration 19 (ratio 4.5); after division of second vagus, pulse 86, respiration 19.

Days since operation.	Pulse.	Respiration.	Ratio.	Days since operation.	Pulse.	Respiration.	Ratio.
1	153 157 165	12.4 14.3 9.7	12.6 10.9 16.2	25	112	24	4.6
2	130	24.0	5.4	28	80	22	3.6
3	140 126 128	28.0 22.0	5.8	32	100	20	5.0
4	135	30.0	4.5	35	100	22	4.5
5	160 144 *	48.0 19.0 *	3.3 7.5	40	105	22	4.7
6	119 130	19.8	6.0	42	112	24	4.6
7	146 † 107	25.0 †	5.2	45	108	26	4.1
9	163 † 140	19.0 †	8.5	49	82	18	4.5
10	115	45.0	2.5	56	94	18	5.2
11	150 140	30.0	4.7	63	102	28	3.6
12	140	34.0	4.1	70	96	20	4.8
13	128	28.0	4.6	77	106	20	5.3
14	100	26.0	3.8	84	104	22	4.7
17	114	50.0	2.3	91	112	24	4.6
18	85	30.0	2.8	124	86	20	4.3
19	112	38.0	3.0	161	90	19	4.7
21	110	30.0	3.6	300	130 †		

* A large abscess due to infection by the syringe used to inject morphia was opened in the morning. The counts indicated by the asterisk were taken in the afternoon. Before the abscess was opened the pulse, and especially the respiration, were accelerated. In ordinary dogs after double vagotomy no such extraordinary acceleration of the respiration was ever seen.

† Animal excited so that the respiration could not be counted.

Athens may have had something to do with this result I forbear to speculate. Undoubtedly in my experience, as in that of others, a sudden drop in the external temperature or other unfavorable climatic change does sometimes appear to determine the onset of the fatal terminal pneumonia, for example in the experiment of January 9, 1897 (Table I). But I have seen no reason to believe that the result is in any essential respect modified by the lapse of even a long time between the division of the two nerves, provided, of course, it is not long enough for effective regeneration to have occurred. I agree with Friedenthal [23] that such a substitution of the influence of one vagus by the other paths as will render the elimination of the second vagus compatible with long life is not realized, at least under our conditions. For instance, in Experiments 14 and 23 (Table II), 59 days elapsed between the first and the second operation, yet the animals died on the second and fourth days respectively after division of the second vagus. In a bitch whose right vago-sympathetic was cut on January 23, 1901, and the left vago-sympathetic on June 8th of the same year (interval of 136 days), the animal was found dead and in rigor on June 10th. The pulse rate before the anæsthetic was given for the second operation was 88, and the rate of respiration 20 (ratio, 4.4 : 1). Under the anæsthetic before section of the left vago-sympathetic, the rates were 60 and 10 respectively; after section of the nerve 180 and 7 (ratio, 25.7 : 1).

I do not propose to discuss here the somewhat discordant views which have been taken by different observers of the cause or causes of death after double vagotomy. Two main groups may be distinguished, — those who lay stress on the pulmonary changes (so-called "section pneumonia"), so frequently seen at autopsy, and those who emphasize the digestive troubles. There can be no doubt that the immediate cause of death is often the pulmonary lesion, and Pawlow [24] and others have shown that when infection of the lungs by the entrance of swallowed or vomited matter is avoided, as by leaving one recurrent laryngeal intact to innervate the muscles that provide for closure of the glottis, or by first making a double œsophageal and gastric fistula, dogs may survive indefinitely. It may be quite clearly demonstrated, however, in animals which live for some weeks after complete section of the vagi in the neck, that notwith-

[23] FRIEDENTHAL: Archiv für Physiologie, 1902, p. 137.

[24] For the literature see KATSCHKOWSKY: Archiv für die gesammte Physiologie, *loc. cit.*

standing the paralysis of the glottis associated with aphonia, no pulmonary symptoms may be present till a day or two before death. The picture presented in these cases is that of an animal suffering above all from alimentary disturbances, difficult deglutition, frequent and persistent vomiting, and progressive emaciation in spite of an appetite which is sometimes ravenous. The animal appears to be slowly starving to death because of the difficulty of swallowing, retaining, and digesting its food. The respiration is, to be sure, very different from the normal in frequency, depth, and type, but there is nothing to suggest that the lungs are the seat of any pathological process. Suddenly the picture changes. Pulmonary symptoms obtrude themselves. The physical signs of consolidation may be detected, and in a short time the animal is inevitably dead. Sometimes, as has been mentioned, the determining cause of the pulmonary lesion seems to be some external circumstance, as a sudden fall of temperature. The idea is exceedingly apt to present itself to the observer that the pneumonia is an accident, an acute intercurrent affection breaking the course of a chronic malnutrition, which in any case must have ended in death, unless the disturbances in the functions of the alimentary canal could have been met, as in Pawlow's experiments, for instance, by direct gastric feeding through a fistula. Of course the vagotomized animal is predisposed to this accident, but there is no definite time after section of the nerves at which it must take place.

The cause of the regurgitation of partially swallowed food which is present in addition to true vomiting has generally been supposed to be the accumulation of the food in the lower part of the paralyzed œsophagus. Cannon[25] states that in the cat elimination of the vagus fibres for the œsophagus only causes a temporary paralysis of the peristaltic movements of the lower part of the tube which is provided with unstriped muscular tissue, although the upper part remains permanently paralyzed. There is no doubt that in the dog swallowing remains difficult, although food can be forced into the stomach after the first few days. The muscles of the mouth and pharynx concerned in deglutition can be observed to contract more persistently than normal, as if struggling with the morsel. There is a good deal of difference in different vagotomized dogs in the case with which food is swallowed. In the exceptional "immune" cases the power of satisfactory deglutition returns early.

[25] CANNON: This journal, 1907, xix, p. 436.

As to the explanation of the existence of such cases, little that is satisfactory can be said. Their rarity is great, and the absence of any sign by which they can be distinguished beforehand are obstacles to their study which one has been unable to overcome. The possibility, a slender one, that exceptionally early regeneration might take place where the severed ends of the nerves or of one of them were specially well situated with regard to each other, led to a series of experiments on twelve dogs, in which one vagus or vago-sympathetic was divided wholly or partially with as little disturbance of the relations as possible and with the sharpest possible edge. In some of the experiments where the nerve was totally divided, the head was kept fixed during and for some time after the operation by mechanical arrangements, so as to prevent retraction of the fragments. The following extracts from the protocols will illustrate the results:

February 25, 1901. — Total section of left vago-sympathetic with small, narrow knife, without disturbing relations.

March 2. — Killed dog. The ends of the nerve were separated by not more than 6 mm., and lay well in line with each other and in contact with carotid. Stimulation of upper end before death caused no effect on the pupil, and stimulation of the lower end no effect on the heart.

February 25, 1901. — Another dog. Divided left vago-sympathetic completely without separating it from the carotid. Neck bent while cutting the nerve, and for some time after.

March 5. — Occasionally makes sound of vomiting, although never actually vomits.

March 6. — Killed. The ends of the nerve are not separated at all. They lie quite in line and are united by grayish material. A casual examination might not show that the nerve had been divided, although when it is fully exposed the scar is seen. Results of stimulation the same as in the other dog operated on on the same day.

March 8, 1901. — Divided left vago-sympathetic with a razor, inserting an aneurism needle between the nerve and the carotid and cutting on the needle. A thin strand of nerve sheath was left uncut.

March 16. — The nerve was found united, with only a narrow scar and slight thickening central to the scar. The cardio-inhibitory and pupillo-dilator fibres were quite inexcitable.

In a second experiment on March 8, 1901, the left vago-sympathetic was completely divided in the same way. On March 16 the ends were seen to lie close together, and united by a narrow band of whitish material. The nerve looked as if only a nick had been made in it, although

there is no doubt that it was completely divided. Stimulation had the same effect as in the first dog operated on on March 8.

In a third dog operated on on March 8, 1901, in the same way a gap of about 12 mm. was found on March 12 between the ends. Stimulation of the lower end causes stoppage of the heart, stimulation of the upper end marked dilation of the pupil.

In another dog 6 days after section of the vago-sympathetic stimulation of the lower end caused acceleration of the heart, the inhibitory fibres having degenerated sooner than the accelerators which run in the vagus.[26]

These results confirm the foregone conclusion that preternaturally rapid regeneration of the divided vagus is not the explanation of the exceptional cases of survival. Another suggestion is that a sufficient number of fibres necessary for life may in these dogs, owing to some anatomical vagary, escape section when the vagi are divided. It is known that some of the fibres usually carried in the vagus may run an aberrant course, efferent cardio-inhibitory fibres, for example, being occasionally present in the rabbit's depressor. May it not be that a part of the motor fibres of the larynx and œsophagus usually running in the recurrent laryngeals may leave the main trunk by the superior laryngeals? This would explain the absence of paralysis of the glottis, and the greater efficiency of the deglutition mechanism after vagotomy, which would be sufficient to account for the more favorable position of the animal, particularly if associated with such an abnormal course of, say, a portion of the Hering-Breuer and the cardio-inhibitory fibres as permitted a sufficient proportion of these to be spared.

In connection with this question and also on account of the interest of the problem in other relations, a series of experiments was made in which one vagus was completely divided, while varying fractions of the total cross section of the other were severed, in order to determine how small a proportion must remain uncut to prevent death. J. Steiner[27] stated that in the rabbit the efferent fibres going to muscle (cardio-inhibitory, œsophageal, and laryngeal fibres) occupy a position on the median side of the vagus, while the afferent (pulmonary) fibres which affect the respiration are contained in a lateral bundle, which it is possible to separate with a thin instrument

[26] *Cf.* Schiff: Archiv für die gesammte Physiologie, 1878, xviii, p. 172; Arloing: Archives de physiologie normale et pathologigue, 1896, viii, 5e serie, p. 75.

[27] Steiner, J.: Archiv für Physiologie, 1878, p. 218.

from the median bundle. At the level of the medulla oblongata the cardio-inhibitory fibres run in the middle and lowermost rootlets of the 9th, 10th, and 11th cranial nerves, and the afferent respiratory fibres in the uppermost rootlets. Cadman [28] has shown that in the dog the afferent respiratory fibres and the afferent cardio-inhibitory fibres enter the bulb in the upper rootlet of the 9th, 10th, and 11th cranial nerves. The efferent cardio-inhibitory fibres leave the bulb in the lowest rootlet. In the cat, although the rootlets are more numerous, the various groups of fibres occupy similar positions. Friedenthal [29] has taken advantage of these facts to eliminate all the extrinsic nerves of the heart without causing death.

So far as I am aware, the precise distribution in the vagus trunk of the dog of the various functional groups of fibres is unknown. Judging from the similarity of the paths in the rootlets of the rabbit and dog, it is not very hazardous to assume that the efferent cardio-inhibitory fibres are probably mainly at the median side, and the afferent respiratory fibres mainly at the external side of the nerve. A larger or smaller part of the cross section was therefore divided, beginning either at the median or at the lateral side of the nerve, the amount actually cut being controlled by micrometric measurements on the hardened material obtained *post mortem*. Several dogs were operated on with aseptic technique. In one of these (a young male fox terrier) the vagi were slightly separated with a needle from the sympathetics in the neck. Rather more than half the cross section of the right vagus proper, beginning at the median side, was divided. The partial section of the right vagus caused no change in the pulse rate (138); the respiratory frequency slightly diminished (from 41 to 36). Then the left vagus was completely divided. The effect on the pulse rate (increase to 177) on the respiration (diminution to twelve a minute with deep, prolonged inspiration), and on the voice indicated that all the cardio-inhibitory fibres, many of the Hering-Breuer fibres, and a part of the motor supply of the glottis muscles in the right vagus had been cut. This would suggest that the cardio-inhibitory fibres lie at the median side of the nerve and the Hering-Breuer fibres at the lateral side, as Steiner says is the case in the rabbit. The wound healed by first intention. The animal recovered entirely and was killed for autopsy after 55 days. Among the symptoms in regard to which this animal

[28] CADMAN: Journal of physiology, 1900, xxvi, p. 42.
[29] FRIEDENTHAL: Archiv für Physiologie, 1902, p 135.

in the first days after the operation conformed to the classical clinical picture of double vagotomy were the greatly accelerated pulse and the diminished respiratory frequency. A striking difference was the rapid restoration of a normal rate of respiration and a normal pulse rate. (Respiration on the following day 20, pulse rate 126; on the second day 20 and 139; on the fifth day 22½ and 104 respectively.) As regards the digestive tract, the animal swallowed without difficulty from the first, indicating the escape of a portion at any rate of the œsophageal motor fibres, which therefore do not, it is to be supposed, all lie at the median side of the dog's vagus, as Steiner states is the case in the rabbit. There is some possibility, perhaps, that a larger portion of gullet is provided with smooth muscle which sooner recovers its power of peristalsis in some dogs than in others. Nevertheless there was some gastro-œsophageal disturbance indicated by numerous abortive attempts at vomiting, accompanied by the characteristic sound, repeated at generally increasing intervals during the first four weeks. Actual vomiting or regurgitation, which forms so constant a symptom after total section of both vagi, was never seen. Partial aphonia was present for a while, the attempted whine or bark being shriller than usual. Frequent hawking or coughing was observed from the end of the second till the end of the fourth week, possibly excited by some irritation arising in the partially severed nerve. On the second, third, and fourth days there were several peculiar convulsive attacks, never seen, in my experience, in dogs after total vagotomy. The animal would fall down on the floor on its back, the limbs extended in spasm, with moderate opisthotonus and twitching of the eyelids. Consciousness was not lost. The anal sphincter was relaxed. The heart was decidedly slowed (to 92 a minute immediately after one attack and 96 a minute after another). The animal soon got up, but was weak on its legs for some time. The normal acceleration of the heart towards the end of inspiration was already present on the day after the operation. After total section it is not seen. Apparently a small number of vagal cardio-inhibitory fibres had been spared. The number could not have been large, since the heart after the operation was accelerated to the rate ordinarily seen after total vagotomy. It is interesting that the removal or diminution at the time of the inspiratory acceleration of the cardio-inhibitory tone maintained by this relatively small number of fibres should produce a very distinct effect. However, it has never been demonstrated that the accelerator fibres in the vagus may not be concerned in this acceleration.

Another young dog died in less than three days with the typical symptoms seen after complete section of both vagi, although somewhat less than one third of the total diameter of one vagus proper remained uncut on the external side (total diameter, 71; uncut portion, 23). On the day after the operation the pulse was 164 in the morning, 180 in the evening, and the respiration 8. Vomiting was frequent, and deglutition difficult. Aphonia was present.

In other experiments the vagi were divided piecemeal and the effects of successive partial sections on the pulse and respiration observed. Thus in the experiment of January 25, 1905, in a dog under morphia and ether, the following observations were made:

	Pulse	Respiration
Both vago-sympathetics exposed	102	25.3
	94	22.6
Cut $\frac{1}{2}$ of left v. s. from outer side	96	21.3
Cut $\frac{2}{3}$ of left v. s. from outer side	110	21.3
	114	21.3
Cut through left v. s.	114	17.3
	116	18.6
Cut more than $\frac{1}{3}$ of right v. s. from median side .	116	19
	116	19
Cut $\frac{2}{3}$ of right v. s. from median side	184 [80]	14.6
	182 [80]	13.6
Cut through right v. s.	184 [80]	13
	200	12.8

Another set of experiments was made in which the vagus was stimulated above or below the level at which successive partial sections had been made, in order to study the quantitative differences in the effects produced on the pulse rate, the respiration and blood pressure by stimulation of given strength when the proportion of the total cross section of the nerve stimulated was varied.

Experiment of February 13, 1905, is an example. A large dog was anæsthetized with ACE mixture. The left vagus was isolated from the sympathetic. The sympathetic was cut and the lower end stimulated. No effect on the heart was caused by the stimulation. The peripheral end of the isolated vagus was now stimulated (by shielded electrodes fixed

[80] These pulse counts are somewhat too low, as a weak beat was missed occasionally in the femoral artery, where the pulse was counted. In the last observation it was counted over the thorax.

once for all in position on the nerve) with a strength of current sufficient to stop the heart completely. Made a partial section of the vagus below the electrodes extending a little more than one-third across, beginning at the median side. Stimulated vagus with same current as before; the heart is now only slowed, not stopped. Increased the strength of the stimulus, the heart is stopped. Deepened the cut (Post mortem it was shown by hardening the nerve and measuring the total section [31] and the uncut portion of the section that the ratio between them was 11.8 : 4.8, so that about three-fifths of the fibres were severed). Stimulation with the weaker current previously used caused no effect whatever on the heart. The stronger stimulation caused standstill. Now made a second cut a little lower down on the nerve than the first, but beginning at the outer side, and dividing about one-third of the total section of the nerve. No effect on the heart is caused by stimulation with the weaker stimulus used before. Now made a third cut one-third of an inch below the second, beginning at the median side of the nerve and involving between one-fourth and one-third of the total section. Stimulation at the same position as before with the stronger stimulus caused stoppage of the heart. Deepened this cut so as to include rather more than one-half the section of the nerve. Stimulation with the stronger current causes stoppage of the heart. Deepened the cut somewhat. The stronger stimulus has now no effect on the heart. Since the various portions of the nerve are still in physical contact with each other, none of the previous inhibitory effects are to be attributed to escape of current below the incisions or to electrotonic currents. A still stronger current causes stoppage of the heart. Deepened the third cut so as to leave only between one-eighth and one-ninth of the total cross section undivided (as shown by *post mortem* measurement). Stimulation with the strongest current has *no* effect on the heart.

In some experiments one vagus or vago-sympathetic was stimulated without dividing it, and then partial sections were made above or below the point of stimulation. The other vagus was either intact or previously divided. The conflicting or conspiring effects of simultaneous excitation of efferent and afferent fibres in the nerve were sometimes analyzed in an interesting way by means of the partial sections. For instance, in the

Experiment of January 10, 1905, the left vago-sympathetic of a dog anæsthetized by chloretone and ether was stimulated without division, a

[31] By making outlines of the sections with the camera lucida, cutting out patterns from thin sheet copper and weighing them, and also by measuring various diameters with the eyepiece micrometer.

blood-pressure tracing being taken from the carotid. The relations of the nerve were not disturbed, and the other vago-sympathetic was left intact. Both with weak and strong stimulation slowing of the heart and a slight fall of blood pressure were obtained. The nerve was then partially divided below the level of the electrodes, the cut beginning at the median (vagal) side and extending fully half-way across the vago-sympathetic. Stimulation with the strong stimulus used before caused slowing of the heart and only a slight fall of pressure The cause of the small effect on the pressure was revealed on deepening the cut, for stimulation was now without effect on the heart rate but caused a marked increase of pressure, the afferent pressor fibres being now permitted to prevail over the efferent inhibitory fibres. The left vago-sympathetic was then completely divided. The pulse was now 146, the respiration 22. Partial section of the vago-sympathetic beginning at the median side reduced these rates to 140 and 20. A further cut left the pulse rate unchanged, but reduced the respiratory rate to 18. On increasing the depth of the cut still further, the pulse rate rose to 150, the maximum seen in the experiment, even after total section of the right vago-sympathetic somewhat later, and the respiratory frequency sank to 14, the minimum rate. Although the increase of the pulse rate to the maximum might seem to indicate that all the cardio-inhibitory fibres had been divided, this was not the case, since stimulation of the nerve above the cut still caused some slowing of the heart, with a slight fall of blood pressure and stoppage of respiration. When the cut was extended still more, stimulation no longer produced any effect upon the heart, but caused a slight fall of blood pressure, after a longer latent period than the fall previously obtained, and probably due to the excitation of depressor fibres.

Good evidence was obtained in several of the experiments that while inhibitory effects can be produced on the heart by excitation of a relatively small proportion of the total number of cardio-inhibitory fibres, the threshold is raised when the proportion is reduced beyond a certain limit, and further that the effect produced is less profound and more transient. The period of recovery of the heart when it has begun to beat again is especially shortened when the number of inhibitory fibres is reduced, even when the stoppage of the heart is as prompt and its complete quiescence as prolonged as before. For this reason the fall of blood pressure caused by cardiac inhibition produced by excitation of a limited number of inhibitory fibres, even where the inhibition is complete, is less persistent than where a greater number of fibres have been excited. Thus, in the experiment of February 7, 1905, the right

vago-sympathetic of a dog anæsthetized with morphia and ACE was exposed and the strength of stimulation determined which just caused stoppage of the heart. A partial section was now made below the electrodes, beginning at the median (vagal) side and extending between one-third and one-half way across the nerve. The pulse rate was 86 and the respiratory rate 32.8 before the section, 82 and 27.4 respectively after it. Stimulation of the same strength stops the heart only for an instant. It requires a stronger stimulus to cause stoppage as complete and lasting as long as that caused before section. When the peripheral end of the left vago-sympathetic was stimulated with such a strength of current as caused complete inhibition of the heart, no inhibitory effect was obtained after a section of the nerve below the position of the electrodes, beginning at the lateral (sympathetic) side and dividing everything except about one-tenth of the total cross section of the vagus proper at the median side. The existence of accelerator fibres in the vagus of the dog was clearly demonstrated in many of the experiments, and indications were observed that an effective proportion of them may escape section when all or nearly all the inhibitory fibres have been cut. For example, in the experiment just referred to, when the peripheral end of the vago-sympathetic was stimulated the heart was stopped, and when it resumed beating after stimulation was ended there was distinct acceleration, as is very commonly observed in dogs. A partial section, beginning at the median side and extending nearly one-third across the vagus proper, was now made below the level of the electrodes. Stimulation of the same strength caused the same effects as before. But when the cut was extended so as to sever about one-half of the vagus proper, the same stimulation caused only slight slowing of the heart, although quite as great an after-acceleration as before the section.

One or two similar experiments on partial stimulation of the afferent fibres in the sciatic which influence the blood pressure and the respiration were performed, although not enough to permit any very definite conclusions to be drawn. In a dog anæsthetized with chloretone and ether the central end of the sciatic was stimulated (after section of both vago-sympathetics) with strong induction shocks. The respiration was markedly quickened, then slowed, and there was a slight fall of blood pressure. The nerve was now partially divided centrally to the electrodes. Stimulation of the

same strength as before caused no change in the blood pressure, but the same respiratory effects as previous to the section. On deepening the cut and repeating the stimulation, slowing of the respiration without previous acceleration was obtained. This apparent reversal of the original effect may be due to the escape of a group of inhibitory respiratory fibres, while the fibres which accelerate the respiration have been cut. It is also conceivable, however, that the excitation of a relatively small number of afferent fibres might so affect the respiratory centre as to reduce the rate of its discharge, while stimulation of a larger number of similar fibres might increase that rate, just as stimulation of one and the same group of fibres may have different effects according to the strength of the stimulus.

Summary.

1. After double vagotomy in dogs the ratio of the pulse rate to the respiratory rate, which is at first much increased through the quickening of the heart and slowing of respiration, tends to diminish, as time goes on, in animals which survive more than two or three days. This change is due to a fall in the pulse rate, the rate of respiration in the great majority of cases showing no tendency to increase.

2. The relative constancy of the respiratory rate after double vagotomy depends largely on the fact that in the absence of the Hering-Breuer fibres the fundamental rhythm of the respiratory centre becomes predominant.

3. This fundamental rhythm is revealed in the initial rate of respiration in resuscitation after anæmia of the brain and cervical cord before the afferent paths to the respiratory centre have been opened up. The initial rate (about four a minute) has been studied mainly in cats; but it appears to be remarkably constant not only in different individuals of the same species, but in the different mammalian species investigated (dog, cat, rabbit).

4. At a certain stage in resuscitation, after respiratory movements have returned, an artificial rhythm may be impressed upon the respiratory centre through the pulmonary vagus fibres, by inflating and deflating the lungs at a given rate. The breathing becomes exactly synchronous with the artificial respiration, and persists at the acquired rate for some time after the artificial respiration is stopped.

5. The rate of the heart when isolated from its extrinsic nerves by cerebral anæmia is relatively constant when the external conditions (for instance, the temperature and pressure of the blood) are kept constant.

6. The fatal result of double vagotomy in dogs is not obviated when a considerable interval is allowed to elapse between division of the two vagi.

7. In very rare cases dogs may recover completely after simultaneous bilateral vagotomy above the origin of the recurrent laryngeals. This result is not connected with any specially favorable situation of the ends of one or both of the divided nerves which ensures prompt regeneration. It may be due to some anatomical peculiarity.

8. When one vagus was divided completely and somewhat more than one-half of the other (beginning at the median side, and thus sparing to a great extent the Hering-Breuer fibres), a dog recovered completely. When somewhat less than one-third of the total diameter of the second vagus remained uncut (at the external side), another dog died with all the usual symptoms of complete vagotomy.

9. When one vagus is stimulated and partial sections of the nerve increasing successively in depth are made between the electrodes and the heart, evidence is obtained that up to a certain point excitation with a given strength of stimulus produces the same effect upon the heart whether all the cardio-inhibitory fibres in the nerve are stimulated, or only a certain number. Beyond this point the inhibitory effect is diminished, but can be made as great as before by increasing the strength of the stimulus. Beyond this, again, no increase in strength of stimulation suffices to cause the same inhibitory effect. When a relatively small number of cardio-inhibitory fibres is excited, the heart may stop as promptly as when all are excited, but it recovers more rapidly.

I have to thank my friend Dr. F. H. Pike for correcting the proof in my absence.

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